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FILE 'HOME' ENTERED AT 14:51:20 ON 20 NOV 2001

=> file ca

=> s rar and modulat?
          2813 RAR
        218135 MODULAT?
L1         362 RAR AND MODULAT?

=> s b or beta
       1126519 B
       1021677 BETA
L2     1995134 B OR BETA

=> s l2 and rar
          2813 RAR
L3         1365 L2 AND RAR

=> s rar (2a) l2
          2813 RAR
L4         1009 RAR (2A) L2

=> s l1 and l4
L5          149 L1 AND L4

=> s l5 and antagon?
        208328 ANTAGON?
L6           16 L5 AND ANTAGON?

=> d ibib abs 1-16

L6   ANSWER 1 OF 16  CA  COPYRIGHT 2001 ACS
ACCESSION NUMBER:        134:305279  CA
TITLE:                   Methods of identifying compounds having nuclear
                         receptor negative hormone and/or antagonist
                         activities
INVENTOR(S):             Klein, Elliott S.; Nagpal, Sunil; Chandraratna,
                         Roshantha A.
PATENT ASSIGNEE(S):      Allergan Sales, Inc., USA
SOURCE:                  U.S., 100 pp., Cont.-in-part of U.S. Ser. No. 928,552,
                         abandoned.
                         CODEN: USXXAM
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  6
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     --------------    ----  --------       ---------------  --------
     US 6218128         B1   20010417       US 1998-42943    19980317
     US 5776699         A    19980707       US 1996-613863   19960311
     EP 931786          A2   19990728       EP 1998-204074   19960823
     EP 931786          A3   19990901
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI
     US 6228848         B1   20010508       US 1999-447082   19991122
PRIORITY APPLN. INFO.:                  US 1995-522778   A  19950901
                                        US 1995-522779   A  19950901
                                        US 1995-542648   A  19951013
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	US 1996-613863	A	19960311
	US 1997-928552	B2	19970912
	US 1995-19015	P	19950901
	US 1995-64853	P	19950901
	US 1995-20501	P	19951013
	EP 1996-933742	A3	19960823
	US 1997-871093	A3	19970609
	US 1998-222983	A3	19981230

AB Methods of characterizing and identifying neg. hormones of nuclear receptors are disclosed. Also disclosed are methods of making **modulators** of retinoid nuclear receptor transactivation activity, assays for agonists, **antagonists**, and neg. hormones of the **RAR** receptor, and specific retinoid **modulators** of retinoid nuclear receptors.

REFERENCE COUNT: 234

REFERENCE(S):
(1) Agarwal; Cancer Research V54, P2108 CA
(2) Agarwal; Cancer Research V51, P3982 CA
(3) Allegretto; The Journal of Biological Chemistry 1993, V268(35), P26625 CA
(4) Andreatta-van Leyen; Journal of Cellular Physiology 1994, V160, P265 CA
(5) Anon; DE 3316932 1983 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 16 CA COPYRIGHT 2001 ACS

ACCESSION NUMBER: 134:125954 CA

TITLE: Use of **RAR antagonists** as **modulators** of hormone-mediated processes

INVENTOR(S): Evans, Ronald M.; Tontonoz, Peter J.; Nagy, Laszlo

PATENT ASSIGNEE(S): The Salk Institute for Biological Studies, USA

SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001003659	A1	20010118	WO 2000-US18543	20000707

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1999-352816 A 19990713

AB Retinoic acid receptor (**RAR**) **antagonists** are capable of **modulating** processes mediated by other members of the steroid/thyroid hormone receptor superfamily, including permissive receptors such as PPARs (e.g., PPAR.alpha., PPAR.delta. and PPAR.gamma.). It has been discovered that **RAR antagonists**, in combination with agonists for members of the steroid/thyroid hormone receptor superfamily, are capable of inducing and/or enhancing processes mediated by such members.

REFERENCE COUNT: 11

REFERENCE(S):
(1) Bernardon; US 5574036 A 1996 CA
(2) Bernardon; US 5786379 A 1998 CA
(3) Bernardon; US 5798354 A 1998 CA
(4) Bernardon; US 5952382 A 1999 CA
(5) Boehm; US 5780676 A 1998 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 16 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 134:98853 CA
TITLE: Differentiation-independent retinoid induction of folate receptor type .beta., a potential tumor target in myeloid leukemia
AUTHOR(S): Wang, Hui; Zheng, Xuan; Behm, Frederick G.; Ratnam, Manohar
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Medical College of Ohio, Toledo, OH, 43614-5804, USA
SOURCE: Blood (2000), 96(10), 3529-3536
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Folate receptor (FR) type .beta. is expressed in the myelomonocytic lineage, predominantly during neutrophil maturation and in myeloid leukemias. FR-.beta. expression was elevated up to 20-fold by all-trans retinoic acid (ATRA) in KG-1 myeloid leukemia cells in a dose-dependent and reversible manner in the absence of terminal differentiation or cell growth inhibition. ATRA also increased FR-.beta. expression in vitro in myeloid leukemia cells from patient marrow. FR-.beta. was not up-regulated in KG-1 cells treated with phorbol ester, dexamethasone, 1,25-dihydroxy vitamin D3, or transforming growth factor .beta.. ATRA did not induce FR-.beta. expression in receptor neg. cells of diverse origin. The ATRA-induced increase in FR-.beta. expression in KG-1 cells occurred at the level of mRNA synthesis, and in 293 cells contg. a stably integrated FR-.beta. promoter-luciferase reporter construct, ATRA induced expression of the reporter. From expts. using retinoid agonists and **antagonists** and from contransfection studies using the FR-.beta. promoter and expression plasmids for the nuclear receptors retinoic acid receptor (**RAR**).alpha., **RAR**.**beta**., or **RAR**.gamma., it appears that the retinoid effect on FR-.beta. expression could be mediated by ligand binding to RARs .alpha., .beta., or .gamma., but not to retinoid X receptors. Furthermore, there was apparent cross-talk between **RAR**.alpha. and **RAR**.gamma. selective agonists or **antagonists**, suggesting a common downstream target for **RAR** isoforms in inducing FR-.beta. expression. Thus, blocks in the **RAR**.alpha.-specific pathway of retinoid-induced differentiation may be bypassed during retinoid induction of FR-.beta. expression. The results suggest that to facilitate FR-targeted therapies, retinoids may be used to **modulate** FR-.beta. expression in myeloid leukemia cells refractory to retinoid differentiation therapy.

REFERENCE COUNT: 51
REFERENCE(S): (1) Bolton, J; Gene 1999, V230, P215 CA
(4) Delva, L; Blood 1993, V82, P2175 CA
(6) Douer, D; Exp Cell Res 1982, V138, P193 CA
(7) Fanelli, M; Blood 1999, V93, P1477 CA
(8) Fanjul, A; Nature 1994, V372, P107 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 16 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 133:305372 CA
TITLE: Induction of apoptosis in ovarian carcinoma cells by AHPN/CD437 is mediated by retinoic acid receptors
AUTHOR(S): Holmes, William F.; Dawson, Marcia I.; Soprano, Dianne Robert; Soprano, Kenneth J.
CORPORATE SOURCE: Department of Microbiology & Immunology, Temple University School of Medicine, Philadelphia, PA, 19140, USA
SOURCE: J. Cell. Physiol. (2000), 185(1), 61-67

CODEN: JCLLAX; ISSN: 0021-9541
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Retinoids have great promise in the area of cancer therapy and chemoprevention. These natural and synthetic derivs. of vitamin A have been shown to play an important role in regulating cell differentiation and proliferation. While all-trans-retinoic acid (ATRA) has been demonstrated to inhibit the growth of several ovarian tumor cell lines, other ovarian carcinoma cell lines have been found to be resistant to retinoid dependent growth suppression. Interestingly, a novel synthetic retinoid, CD437 or AHPN, has been demonstrated to inhibit the growth of both ATRA-sensitive (CA-OV3) and ATRA-resistant (SK-OV3) ovarian tumor cell lines as well as to induce apoptosis. The overall goal of this research was to understand the mechanism by which AHPN/CD437 induces apoptosis in ovarian tumor cell lines. Since a no. of studies have demonstrated the importance of nuclear receptors (RARs and RXRs) in mediating cellular responses to retinoids, we wished to det. the role of RARs in mediating the AHPN/CD437 response. We **modulated** **RAR** level and function by overexpressing either wild type **RAR**-.gamma. or a pan dominant neg. mutant of all **RAR** subtypes called **RAR**-.**beta**. (R269Q), or through the use of an **RAR**-.gamma. **antagonist**, MM11253. We found that inhibition of **RAR** function reduced but did not eliminate induction of apoptosis in both CA-OV3 and SK-OV3 cells by AHPN/CD437. Likewise, overexpression of wild type **RAR**-.gamma. was found to increase apoptosis after treatment with AHPN/CD437. Our results suggest that in ovarian carcinomas, AHPN/CD437 induced apoptosis is mediated at least in part via an **RAR** pathway.

REFERENCE COUNT: 36
REFERENCE(S):
(2) Bernard, B; Biochem Biophys Res Commun 1992, V186, P977 CA
(4) Chao, W; Cancer Lett 1997, V115, P1 CA
(6) De Luca, L; FASEB J 1991, V5, P2924 CA
(7) Fanjul, A; Nature 1994, V372, P107 CA
(8) Gudas, L; The Retinoids ed 2 1994, P443 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 16 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 133:275967 CA
TITLE: Dual mechanisms of action of the retinoid CD437: nuclear retinoic acid receptor-mediated suppression of squamous differentiation and receptor-independent induction of apoptosis in UMSCC22B human head and neck squamous cell carcinoma cells
AUTHOR(S): Sun, Shi-Yong; Yue, Ping; Chandraratna, Roshantha A. S.; Tesfaigzi, Yohannes; Hong, Waun K.; Lotan, Reuben
CORPORATE SOURCE: Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA
SOURCE: Mol. Pharmacol. (2000), 58(3), 508-514
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The synthetic retinoid 6-[3-(adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437), which can bind to and activate the nuclear retinoic acid receptors .**beta**. and .gamma.(**RAR**. **beta**./.gamma.), is a potent inducer of apoptosis in various cancer

cell lines. However, this effect was reported to be independent of RARs. In this study, we compared and contrasted the potencies and mechanisms of action of CD437 and several other receptor-selective retinoids in induction of apoptosis and **modulation** of squamous differentiation in UMSCC22B human head and neck squamous cell carcinoma cell line. CD437 and the structurally related retinoid CD2325 exhibited almost equal potency in inducing apoptosis, whereas several other retinoids failed to induce apoptosis. The **RAR**-specific pan **antagonist** AGN193109 failed to suppress CD437-induced apoptosis, indicating that the induction of apoptosis by CD437 was **RAR** -independent. C-Fos expression was induced by CD437 and CD2325 that induced apoptosis in the cell line but not by other retinoids that failed to induce apoptosis, suggesting a role for c-Fos in CD437-induced apoptosis. At low concn. (0.01 .mu.M), CD437 shared with several other receptor-selective retinoids the ability to suppress the mRNA levels of the squamous differentiation markers Spr1, involucrin, and cytokeratin 1. This effect of CD437 could be blocked by AGN193109. We conclude that CD437 can exert its effects in UMSCC22B human human head and neck squamous cell carcinoma cells by at least two mechanisms: **RAR**-mediated suppression of squamous differentiation and **RAR**-independent induction of apoptosis.

REFERENCE COUNT: 35

REFERENCE(S):
(1) Adachi, H; Am J Respir Cell Mol Biol 1998, V18, P323 CA
(2) Bernard, B; Biochem Biophys Res Commun 1992, V186, P977 CA
(3) Blanchet, S; J Invest Dermatol 1998, V111, P206 CA
(4) Bortner, C; Trends Cell Biol 1995, V5, P21 CA
(5) Chambon, P; FASEB J 1996, V10, P940 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 16 CA

ACCESSION NUMBER: 133:202727 CA

TITLE: Identification of receptor-selective retinoids that are potent inhibitors of the growth of human head and neck squamous cell carcinoma cells

AUTHOR(S): Sun, Shi-Yong; Yue, Ping; Mao, Li; Dawson, Marcia I.; Shroot, Braham; Lamph, William W.; Heyman, Richard A.; Chandraratna, Roshantha A. S.; Shudo, Koichi; Hong, Waun K.; Lotan, Reuben

CORPORATE SOURCE: Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA

SOURCE: Clin. Cancer Res. (2000), 6(4), 1563-1573
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Retinoids **modulate** the growth and differentiation of cancer cells presumably by activating gene transcription via the nuclear retinoic acid receptor (**RAR**) .alpha., .**beta**., and .gamma. and retinoid X receptor (RXR) .alpha., .beta., and .gamma.. We analyzed the effects of 38 **RAR**-selective and RXR-selective retinoids on the proliferation of 10 human head and neck squamous cell carcinoma (HNSCC) cell lines. All of these cell lines expressed constitutively all of the receptor subtypes except **RAR**.**beta**., which was detected in only two of them. Most of the **RAR**-selective retinoids inhibited the growth of HNSCC cells to varying degrees, whereas the RXR-selective retinoids showed very weak or no inhibitory effects. Three **RAR antagonists** suppressed growth inhibition by

RAR-selective agonists, as well as by **RAR**/RXR **antagonists** such as 9-cis-retinoic acid. Combinations of RXR-selective and **RAR**-selective retinoids exhibited additive growth-inhibitory effects. Furthermore, we found that CD437, the most potent growth-inhibitory retinoid induced apoptosis and up-regulated the expression of several apoptosis-related genes in HNSCC cells. These results indicate that: (a) retinoid receptors are involved in the growth-inhibitory effects of retinoids; (**b**) RXR-**RAR** heterodimers rather than RXR-RXR homodimer are the major mediators of growth inhibition by retinoids in HNSCC cells; and (c) induction of apoptosis can account for one mechanism by which retinoids such as CD437 inhibit the growth of HNSCC cells. Finally, these studies identified several synthetic retinoids, which are much more effective than the natural RAs and can be good candidates for chemoprevention and therapy of head and neck cancers.

REFERENCE COUNT: 59

REFERENCE(S):
(1) Adachi, H; Am J Respir Cell Mol Biol 1998, V18, P323 CA
(2) Angel, P; Biochim Biophys Acta 1991, V1072, P129 CA
(3) Beard, R; J Med Chem 1995, V38, P2820 CA
(4) Bernard, B; Biochem Biophys Res Commun 1992, V186, P977 CA
(5) Boehm, M; J Med Chem 1994, V37, P2930 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 16 CA COPYRIGHT 2001 ACS

ACCESSION NUMBER: 133:132870 CA

TITLE: An immortalized rat liver stellate cell line (HSC-T6): a new cell model for the study of retinoid metabolism in vitro

AUTHOR(S): Vogel, Silke; Piantedosi, Roseann; Frank, Jorge; Lalazar, Avraham; Rockey, Don C.; Friedman, Scott L.; Blaner, William S.

CORPORATE SOURCE: Department of Medicine, College of Physicians and Surgeons of Columbia University, New York, NY, 10032, USA

SOURCE: J. Lipid Res. (2000), 41(6), 882-893
CODEN: JLPRAW; ISSN: 0022-2275

PUBLISHER: Lipid Research, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Hepatocytes and hepatic stellate cells play important roles in retinoid storage and metab. Hepatocytes process postprandial retinyl esters and are responsible for secretion of retinol bound to retinol-binding protein (RBP) to maintain plasma retinol levels. Stellate cells are the body's major cellular storage sites for retinoid. We have characterized and utilized an immortalized rat stellate cell line, HSC-T6 cells, to facilitate study of the cellular aspects of hepatic retinoid processing. For comparison, we also carried out parallel studies in Hepa-1 hepatocytes. Like activated primary stellate cells, HSC-T6 express myogenic and neural crest cytoskeletal filaments. HSC-T6 cells take up and esterify retinol in a time- and concn.-dependent manner. Supplementation of HSC-T6 culture medium with free fatty acids (up to 300 .mu.M) does not affect retinol uptake but does enhance retinol esterification up to 10-fold. RT-PCR anal. indicates that HSC-T6 cells express all 6 retinoid nuclear receptors (**RAR**.alpha., -. **beta**., -.gamma., and RXR.alpha., -.beta., -.gamma.) and like primary stellate cells, HSC-T6 stellate cells express cellular retinol-binding protein, type I (CRBP) but fail to express either

retinol-binding protein (RBP) or transthyretin (TTR). Addn. of retinol (10-8-10-5 M) or all-trans-retinoic acid (10-10-10-6 M) rapidly up-regulates CRBP expression. Using **RAR**-specific agonists and **antagonists** and an RXR-specific agonist, we show that members of the **RAR**-receptor family **modulate** HSC-T6 CRBP expression. Thus, HSC-T6 cells display the same retinoid-related phenotype as primary stellate cells in culture and will be a useful tool for study of hepatic retinoid storage and metab.

REFERENCE COUNT: 54

REFERENCE(S):
(3) Blaner, W; FEBS Lett 1990, V274, P89 CA
(4) Blaner, W; FEBS Lett 1991, V287, P193 CA
(5) Blaner, W; J Lipid Res 1985, V26, P1241 CA
(6) Blaner, W; Methods Enzymol 1990, V189, P270 CA
(7) Blaner, W; The Retinoids:Biology, Chemistry, and Medicine 1994, P229 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 16 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 133:40913 CA
TITLE: Retinoic Acid Inhibits Nitric Oxide Synthase-2 Expression through the Retinoic Acid Receptor-.alpha.
AUTHOR(S): Sirsjo, Allan; Gidlof, Andreas C.; Olsson, Anneli; Torma, Hans; Ares, Mikko; Kleinert, Hartmut; Forstermann, Ulrich; Hansson, Goran K.
CORPORATE SOURCE: Center for Molecular Medicine, Karolinska Institute at the Karolinska Hospital, Stockholm, S-171 76, Swed.
SOURCE: Biochem. Biophys. Res. Commun. (2000), 270(3), 846-851
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Retinoids are multipotent **modulators** of cellular functions and suppress cytokine-induced prodn. of nitric oxide (NO) in several cell types. We have explored the mechanisms by which retinoic acid (RA) regulates NO prodn. in rat aortic smooth muscle cells (VSMC), which express NOS2 in response to proinflammatory cytokines. RA inhibited interleukin-1.beta. (IL-1.beta.)-induced NOS2 mRNA expression and NO prodn. These effects were attenuated by the retinoic acid receptor (**RAR**) **antagonist** CD3106, indicating that they were mediated through retinoic acid receptors (RARs). The synthetic retinoid agonists CD336 (which specifically binds **RAR**.alpha.) and CD367 (which binds all RARs) but not agonists specific for **RAR**. **beta**., **RAR**.gamma., or RXRs reduced IL-1.beta.-induced NOS2 expression and NO prodn. When transfecting VSMC with a 1570-bp NOS2 promoter fragment fused to a luciferase reporter gene, the NOS2 promoter activity was inhibited by RA. These results indicate that retinoids **modulate** NO prodn. in VSMC via **RAR**.alpha., which inhibits the transcription of the NOS2 gene. (c) 2000 Academic Press.

REFERENCE COUNT: 39

REFERENCE(S):
(1) Becherel, P; J Invest Dermatol 1996, V106, P1182 CA
(3) Bredt, D; Annu Rev Biochem 1994, V63, P175 CA
(4) Chomczynski, P; Anal Biochem 1987, V162, P156 CA
(5) Delescluse, C; Mol Pharm 1991, V40, P556 CA
(6) Eberhardt, W; Biochem Biophys Res Commun 1996, V223, P752 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 9 OF 16 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 133:3151 CA

TITLE: **Modulation** of retinoic acid receptor function alters the growth inhibitory response of oral SCC cells to retinoids
AUTHOR(S): Le, Quan; Dawson, Marcia I.; Soprano, Dianne Robert; Soprano, Kenneth J.
CORPORATE SOURCE: Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine, Philadelphia, PA, 19140, USA
SOURCE: Oncogene (2000), 19(11), 1457-1465
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Retinoids have been shown to inhibit the growth of many human tumor cells including breast, ovarian and squamous cell carcinoma (SCC). While the exact mechanism of retinoid mediated growth suppression is not known, a role for the retinoic acid receptors (RARs) and retinoid X receptors (RXRs) has been established in both the breast and ovarian tumor cell models. We set out to det. if **modulation** of **RAR**/RXR function would alter the retinoid sensitivity of oral SCC cells. We found that the growth of SCC cells was significantly inhibited by treatment with either all-trans-retinoic acid (trans-RA) or the synthetic, conformationally restricted **RAR**.gamma. selective retinoids MM11254 and MM11389. In order to demonstrate a role for **RAR**/RXR function in this process, stable oral SCC cell clones constitutively overexpressing the dominant neg. mutant **RAR**.**beta**.2 (R269Q) were prepd. and shown to exhibit reduced **RAR**/RXR transcriptional transactivation activity. We found that oral SCC cells exhibiting reduced **RAR**/RXR function became resistant to growth inhibition by all-trans-RA, MM11254 and MM11389. Likewise, treatment of oral SCC cells with the **RAR**.gamma. **antagonist** MM11253 was found to block the ability of MM11254 and MM11389 to inhibit SCC cell growth. Thus, **modulation** of **RAR** function through the use of **RAR**-.gamma. selective agonists, an **RAR**-.gamma. selective **antagonist** or a pan-**RAR** dominant neg. mutant significantly alters the growth inhibitory response of oral SCC cells to retinoids.

REFERENCE COUNT: 66
REFERENCE(S):
(1) Aylsworth, C; J Natl Cancer Inst 1986, V76, P339 CA
(3) Bernard, B; Biochem Biophys Res Commun 1992, V186, P977 CA
(5) Caliaro, M; Int J Cancer 1994, V56, P743 CA
(6) Carmichael, J; Caner Res 1987, V47, P936 CA
(8) Chao, W; Cancer Lett 1997, V115, P1 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 16 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 132:58791 CA
TITLE: Retinoid-mediated suppression of tumor invasion and matrix metalloproteinase synthesis
AUTHOR(S): Schoenermark, Matthias P.; Mitchell, Teresa I.; Rutter, Joni L.; Reczek, Peter R.; Brinckerhoff, Constance E.
CORPORATE SOURCE: Dartmouth Medical School, Hanover, NH, 03755, USA
SOURCE: Ann. N. Y. Acad. Sci. (1999), 878(Inhibition of Matrix Metalloproteinases), 466-486
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cancer mortality usually results from the tumor invading the local environment and metastasizing to vital organs, e.g. liver, lung, and brain. . Degrdn. of the extracellular matrix is, therefore, the sine qua non of tumor cell invasion, this degrdn. is mediated mainly by MMPs, and thus, inhibition of MMP synthesis is a target for anticancer agents. Tumor cells must traverse both the basement membrane (type IV collagen) and the interstitial stroma (type I collagen). Therefore, we used SEM to examine the invasive behavior of several aggressive tumor cell lines, A2058 melanoma cells, and SCC and FaDu squamous cell carcinomas through these matrixes; and we monitored the ability of all-trans retinoic acid and several **RAR**-specific ligands to block invasion. We demonstrate that several retinoids, which are specific **RAR** .alpha., .**beta**., or .gamma. agonists/**antagonists**, selectively inhibited MMP synthesis in the three tumor cell lines. However, there was not a common pattern of MMP inhibition by a particular retinoid. For instance, a **RAR**.alpha. **antagonist** suppressed MMP-1 and MMP-2 synthesis in the melanoma cell line, but not in the FaDu or SCC-25 cells. On the other hand, synthesis of MMP-1 and MMP-9 by the FaDu cells was affected hardly at all, while a **RAR**.gamma. **antagonist** reduced the levels of MMP-2. Only all-trans retinoic acid reduced MMP-1 synthesis in these cells. We postulate that the differences may be related to a differential pattern of **RAR** expression in each of these cells, and that the RARs expressed by each cell line may not be targets of these **RAR** specific compds. All-trans retinoic acid is a pan ligand, binding to all three RARs and, therefore, may **modulate** gene expression more generally. We conclude that the power of these new ligands lies in their specificity, which can be directed towards **modulating** expression of certain RARs and, thus, of certain MMPs. By blocking MMP synthesis, retinoids may be effective in cancer therapy by decreasing tumor invasiveness.

REFERENCE COUNT: 32

REFERENCE(S):
(1) Allenby, G; Proc Natl Acad Sci 1993, V90, P30 CA
(3) Blau, H; Nature Med 1997, V3, P612 CAPLUS
(4) Borden, P; Crit Rev Eukaryotic Gene Expression 1997, V7, P159 CA
(5) Brinckerhoff, C; Biochim Biophys Acta 1981, V677, P424 CA
(6) Chambers, A; J Natl Cancer Inst 1997, V89, P1260 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 16 CA COPYRIGHT 2001 ACS

ACCESSION NUMBER: 131:179467 CA

TITLE: Signal relay by retinoic acid receptors .alpha. and .beta. in the retinoic acid-induced expression of insulin-like growth factor-binding protein-3 in breast cancer cells

AUTHOR(S): Shang, Yongfeng; Baumrucker, Craig R.; Green, Michael H.

CORPORATE SOURCE: Nutrition Department, The Pennsylvania State University, University Park, PA, 16802, USA

SOURCE: J. Biol. Chem. (1999), 274(25), 18005-18010
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Neither retinoic acid receptor-.**beta**. (**RAR**. **beta**.) nor insulin-like growth factor-binding protein-3 (IGFBP-3)

is expressed in breast cancer cell line MCF-7. The expression of both proteins can be induced in response to all-trans-retinoic acid (atRA). By using an **RAR**.alpha.-selective **antagonist** (Ro 41-5253), the authors demonstrated that **RAR.beta**. expression was induced by atRA through an **RAR**.alpha.-dependent signaling pathway and that **RAR.beta**. induction was correlated with IGFBP-3 induction. However, MCF-7 cells transfected with sense **RAR.beta**. cDNA expressed IGFBP-3 even in the presence of the **RAR**.alpha.-selective **antagonist** Ro 41-5253. Antisense **RAR.beta**. cDNA transfection of MCF-7 cells blocked atRA-induced IGFBP-3 expression, indicating that **RAR**. **beta**. is directly involved in the mediation of IGFBP-3 induction by atRA. Induction of IGFBP-3 expression by atRA occurs at the transcriptional level, as measured by nuclear run-on assays. Finally, the authors showed that atRA-induced IGFBP-3 is functionally active in **modulating** the growth-promoting effect of IGF-I. These expts. indicate that **RAR**.alpha. and **RAR.beta**., both individually and together, are important in mammary gland homeostasis and breast cancer development. By linking IGFBP-3 to **RAR**. **beta**., the authors expts. define the signal intersection between the retinoid and IGF systems in cell growth regulation and explain why loss of **RAR.beta**. might be crit. in breast cancer carcinogenesis/progression.

REFERENCE COUNT: 47

REFERENCE(S): (1) Adamo, M; Endocrinology 1992, V131, P1858 CA
(2) Agadir, A; Cell Mol Biol 1994, V40, P263 CA
(3) Albiston, A; Endocrinology 1995, V136, P696 CA
(4) Berard, J; FASEB J 1996, V10, P1091 CA
(5) Buckbinder, L; Nature 1995, V377, P646 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 12 OF 16 CA COPYRIGHT 2001 ACS

ACCESSION NUMBER: 129:254522 CA

TITLE: Antiproliferative activity and apoptosis induced by retinoic acid receptor-.gamma. selectively binding retinoids in neuroblastoma

AUTHOR(S): Meister, Bernhard; Fink, Franz-Martin; Hittmair, Anton; Marth, Christian; Widschwendter, Martin

CORPORATE SOURCE: Department of Pediatrics, University of Innsbruck, Innsbruck, Austria

SOURCE: Anticancer Res. (1998), 18(3A), 1777-1786
CODEN: ANTRD4; ISSN: 0250-7005

PUBLISHER: Anticancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Retinoids **modulate** several cell functions and esp. inhibit the growth of tumor cells. Their biol. activity is mediated by retinoic acid receptors (RARs), of which three subtypes (.alpha.,.beta.,.gamma.) have been identified. In human neuroblastoma (NB), reduced endogenous **RAR**-.gamma. expression was suggested to diminish the sensitivity for retinoids, to promote proliferation, and to contribute to the malignant phenotype. To correlate receptor selectivity with in vitro activity, we analyzed the effect of six synthetic retinoids with selectivity for human **RAR**-.alpha./.**beta**./.gamma. on the human LAN-5 NB cell line and compared it with the natural compd. all-trans-retinoic acid (ATRA). Apoptosis was detd. by flow-cytometry using terminaldeoxynucleotidyl transferase to end-label DNA fragments in situ in apoptotic cells. The **antagonist** for **RAR**-. **beta**./.gamma. CD2665 as well as the selective agonists for **RAR**-.alpha. CD336 and **RAR**-.**beta**. CD2019 were

less effective in growth inhibition than ATRA. In contrast, the synthetic **RAR**-.gamma. selective agonists CD437 and CD2325 induced a concn.- and time-dependent antiproliferative effect, which was similar or even more pronounced than ATRA. In contrast to ATRA, the addn. of CD437 and CD2325 did not induce morphol. changes typical of NB cell maturation but resulted in morphol. features consistent with the occurrence of programmed cell death. Flow-cytometric anal. showed that in contrast to ATRA the addn. of CD 437 and CD 2325 results in progressive time-dependent increase of apoptotic cells (25.9% and 57.7% after 72 h). In conclusion, our study demonstrates **RAR**-.gamma. selectively binding retinoids dramatically suppress NB cell growth, primarily by inducing programmed cell death rather than by cell differentiation. Since advanced or disseminated NB tumors endogenously express low levels of **RAR** -.gamma. and lack of apoptosis is involved in tumor progression, **RAR**-.gamma. selectively binding retinoids may be more appropriate retinoids for clin. trials in NB.

L6 ANSWER 13 OF 16 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 122:125228 CA
TITLE: A dynamic balance between ARP-1/COUP-TFII, EAR-3/COUP-TFI, and retinoic acid receptor:retinoid X receptor heterodimers regulates Oct-3/4 expression in embryonal carcinoma cells
AUTHOR(S): Ben-Shushan, Etti; Sharir, Hava; Pikarsky, Eli; Bergman, Yehudit
CORPORATE SOURCE: Hubert H. Humphrey Center Experimental Med. Cancer Res., Hebrew Univ-Hadassah Med. Sch., Jerusalem, 91120, Israel
SOURCE: Mol. Cell. Biol. (1995), 15(2), 1034-48
CODEN: MCEBD4; ISSN: 0270-7306
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Oct-3/4 transcription factor is a member of the POU family of transcription factors and, as such, probably plays a crucial role in mammalian embryogenesis and differentiation. It is expressed in the earliest stages of embryogenesis and repressed in subsequent stages. Similarly, Oct-3/4 is expressed in embryonal carcinoma (EC) cells and is repressed in retinoic acid (RA)-differentiated EC cells. Previously we have shown that the Oct-3/4 promoter harbors an RA-responsive element, RAREoct, which functions in EC cells as a binding site for pos. regulators of transcription and in RA-differentiated EC cells as a binding site for neg. regulators. Our present results demonstrate that in P19 and RA-treated P19 cells, the orphan receptors ARP-1/COUP-TFII and EAR-3/COUP-TFI repress Oct-3/4 promoter activity through the RAREoct site in a dose-dependent manner. While the N-terminal region of the ARP-1/COUP-TFII receptor is dispensable for this repression, the C-terminal domain harbors the silencing region. Interestingly, three different RA receptor-retinoid X receptor (**RAr**-rXR) heterodimers, **RAR**.alpha.:RXR.alpha., **RAR**.**beta** .:RXR.alpha., and **RAR**.**beta**.:RXR.**beta**., specifically bind and activate Oct-3/4 promoter through the RAREoct site in a ligand-dependent manner. We have shown that **antagonism** between ARP-1COUP-TFII or EAR-3/COUP-TFI and the **RAr**-rXR heterodimers and their intracellular balance **modulate** Oct-3/4 expression. Oct-3/4 transcriptional repression by the orphan receptors can be overcome by increasing amts. of **RAr**-rXR heterodimers. Conversely, activation of Oct-3/4 promoter by **RAr**-rXR heterodimers was completely abolished by EAR-3/COUP-TFI and ARP-1/COUP-TFII. The orphan receptors bind the RAREoct site with a much higher affinity than the **RAr**-rXR heterodimers. This high

binding affinity provides ARP-1/COUP-TFII and EAR-3/COUP-TFI with the ability to compete with and even displace **RAr**-rXR from the RAREoct site and subsequently to actively silence the Oct-3/4 promoter. We have shown that RA treatment of EC cells results in up-regulation of ARP-1/COUP-TFII and EAR-3/COUP-TFI expression. Most interestingly, in RA-treated EC cells, the kinetics of Oct-3/4 repression inversely correlates with the kinetics of the ARP-1/COUP-TFII and EAR-3/COUP-TFI activation. These findings are in accordance with the suggestion that these orphan receptors participate in controlling a network of transcription factors, among which Oct-3/4 is included, which may establish the pattern of normal gene expression during development.

L6 ANSWER 14 OF 16 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 118:161683 CA
TITLE: Retinoic acid receptor isoform **RAR**.gamma.1: an **antagonist** of the transactivation of the **RAR.beta**. RARE in epithelial cell lines and normal human keratinocytes
AUTHOR(S): Miquel, C.; Clusel, C.; Semat, A.; Gerst, C.; Darmon, M.
CORPORATE SOURCE: Cell Biol. Dep., Cent. Int. Rech. Dermatol., Valbonne, F-06565, Fr.
SOURCE: Mol. Biol. Rep. (1992), 17(1), 35-45
CODEN: MLBRBU; ISSN: 0301-4851
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The diversity of isoforms of retinoic acid (RA) receptors (RARs) and of DNA sequences of retinoic acid-responsive elements (RAREs) suggests the existence of selectivities in the **RAR**/RARE recognition or in the subsequent gene **modulation**. Such selectivities might be particularly important for RAREs involved in pos. feedback, eg. the **RAR.beta**.RARE. In several epithelial cell lines, reporter constructs contg. the **RAR.beta**.RARE linked to the HSV-tk promoter were transactivated in the presence of RA by endogenous RARs and cotransfected **RAR**.alpha.1 and **RAR**.**beta**.2 isoforms, but not by **RAR**.gamma.1. On the contrary, this latter isoform behaved towards the **RAR**.**beta**.RARE as an inhibitor of the transactivation produced by endogenous RARs and by cotransfected **RAR**.alpha.1 and **RAR**.**beta**.2. **RAR**.gamma.1 also behaved as an **antagonist** of the transactivation produced by cotransfected RXR.alpha.. The natural **RAR.beta**. gene promoter or **RAR.beta**.RARE tk constructs were not activated by the endogenous receptors of normal human keratinocytes (NHK), which are known to contain predominantly **RAR**.gamma.1. It was, however, possible to activate to a certain extent **RAR.beta**.RARE-reporter constructs in NHK by cotransfecting **RAR**.alpha.1, **RAR**.**beta**.2, or RXR.alpha.. The **antagonist** behavior of **RAR**.gamma.1 towards the **RAR.beta**.RARE may explain why in certain cell types such as keratinocytes, **RAR**.**beta**. is neither expressed nor induced by RA.

L6 ANSWER 15 OF 16 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 118:140548 CA
TITLE: Prostaglandin E and 12-O-tetradecanoylphorbol-13-acetate are negative **modulators** of retinoic acid synthesis
AUTHOR(S): Napoli, Joseph L.
CORPORATE SOURCE: Sch. Med. Biomed. Sci., State Univ. New York, Buffalo, NY, 14214, USA

SOURCE: Arch. Biochem. Biophys. (1993), 300(2), 577-81
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Although retinoic acid is an important **modulator** of gene transcription that affects diverse processes during embryonic development and in the adult, no regulators of retinoic acid synthesis have been identified. This work will show that deletion of prostaglandin E1 (PGE1) from the defined medium of confluent Madin-Darby canine kidney (MDCK) cells increased retinoic acid synthesis from retinol as much as twofold. Omitting any one of four other growth factors (cortisol, insulin, transferrin, triiodothyronine) had no effect. Adding PGE1 to confluent cells maintained in its absence caused 71% inhibition of the conversion of retinol into retinoic acid. The ED50 of PGE1 was 70 nM and a max. effect was obsd. by 1.5 h. 12-O-Tetradecanoylphorbol 13-acetate (TPA), an inducer of PGE synthesis in MDCK cells, decreased retinoic acid synthesis by 73%. The ED50 of TPA was 5 nM and at least 4 h were required for a max. effect. TPA inhibited the first and rate-limiting step, the conversion of retinol into retinal, and did not decrease either the conversion of retinal into retinoic acid or the elimination t1/2 of retinoic acid. PGE1 and TPA did not inhibit retinoic acid synthesis completely, nor were their actions additive or synergistic, consistent with more than one pathway of retinoic acid synthesis. Indomethacin did not prevent the TPA effect, suggesting that TPA acts independently of prostaglandin generation. MDCK cells expressed mRNA for retinoic acid receptor-.alpha. and retinoic acid receptor-.beta. constitutively, and neither was induced by retinoic acid, consistent with an advanced state of differentiation. These data identify two **antagonists** of retinoid action, TPA and PGE, as **modulators** of retinoic acid synthesis in a retinoic acid-responsive cell. They also demonstrate the utility of MDCK cells for studying interactions among retinoic acid synthesis, the mechanism(s) of retinoic acid action, and the effects of TPA on retinoic acid synthesis and action.

L6 ANSWER 16 OF 16 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 118:118300 CA
TITLE: Use of steroid or thyroid hormone-responsive elements for regulated expression of cloned genes in animal systems
INVENTOR(S): Sucov, Henry M.; Evans, Ronald M.; Umesono, Kazuhiko
PATENT ASSIGNEE(S): Salk Institute for Biological Studies, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9216546	A1	19921001	WO 1992-US2024	19920313
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
CA 2100584	AA	19920920	CA 1992-2100584	19920313
AU 9216578	A1	19921021	AU 1992-16578	19920313
AU 668683	B2	19960516		
EP 576590	A1	19940105	EP 1992-909468	19920313
EP 576590	B1	20010214		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
JP 06508509	T2	19940929	JP 1992-508797	19920313

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     AT 199169         E    20010215       AT 1992-909468   19920313
PRIORITY APPLN. INFO.:                    US 1991-672530   A  19910319
                                          WO 1992-US2024   A  19920313
```

AB Steroid or thyroid hormone-responsive elements from mammalian genes are cloned and characterized for use in the regulated expression of heterologous genes in animal cells. These response elements differ from those previously described in that the repeated sequences are repeated in tandem rather than as palindromes. A mouse genomic library was screened with a probe derived from the first exon of the gene for the human retinoic acid receptor .beta.. The 5'-upstream region of the clone was used to drive expression of a .beta.-galactosidase reporter gene and the gene introduced into CV-1 cells. Expression of the gene was inducible by exogenous retinoic acid and further analyses narrowed the significant region further. A sequence of a six base-pair tandem repeat with an intervening sequence of 11 base pairs was found in this region.

```
=> s rar.alpha. or rar.gamma. or rar.beta.
          2813 RAR
       1186393 ALPHA
          1503 RAR.ALPHA.
                 (RAR(W)ALPHA)
          2813 RAR
        628626 GAMMA
           625 RAR.GAMMA.
                 (RAR(W)GAMMA)
          2813 RAR
       1021677 BETA
           918 RAR.BETA.
                 (RAR(W)BETA)
L7        1971 RAR.ALPHA. OR RAR.GAMMA. OR RAR.BETA.

=> s rar.alpha.
          2813 RAR
       1186393 ALPHA
L8        1503 RAR.ALPHA.
                 (RAR(W)ALPHA)

=> s rar.gamma.
          2813 RAR
        628626 GAMMA
L10        625 RAR.GAMMA.
                 (RAR(W)GAMMA)

=> s rar.beta.
          2813 RAR
       1021677 BETA
L11        918 RAR.BETA.
                 (RAR(W)BETA)

=> s l8 or l10 or l11
L12       1971 L8 OR L10 OR L11

=> s l12 and antagon?
        208328 ANTAGON?
L13        213 L12 AND ANTAGON?

=> s l13 not l6
L14        198 L13 NOT L6
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=> s l14 and modulat?
        218135 MODULAT?
L15          21 L14 AND MODULAT?

=> d ibib abs 1-21

L15  ANSWER 1 OF 21  CA  COPYRIGHT 2001 ACS
ACCESSION NUMBER:        135:314399  CA
TITLE:                   Detection of variations in the DNA methylation profile
                         of genes in the determining the risk of disease
INVENTOR(S):             Berlin, Kurt; Piepenbrock, Christian; Olek, Alexander
PATENT ASSIGNEE(S):      Epigenomics A.-G., Germany
SOURCE:                  PCT Int. Appl., 636 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                German
FAMILY ACC. NUM. COUNT:  27
PATENT INFORMATION:

     PATENT NO.         KIND  DATE           APPLICATION NO.   DATE
     ---------------    ----  --------       ---------------   --------
     WO 2001077373      A2    20011018       WO 2001-DE1486    20010406
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
             ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
             LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD,
             SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
             ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     WO 2001077373      A2    20011018       WO 2001-XA1486    20010406
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
             ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
             LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD,
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             CF, CG, CI, CM, GA, GW, ML, MR, NE, SN, TD, TG
     WO 2001077373      A2    20011018       WO 2001-XB1486    20010406
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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             LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD,
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             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             CF, CG, CI, CM, GA, GW, ML, MR, NE, SN, TD, TG
     WO 2001077373      A2    20011018       WO 2001-XC1486    20010406
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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             ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
             LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD,
             SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA,
             ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
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CF, CG, CI, CM, GA, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: DE 2000-10019058 A 20000406
WO 2001-DE1486 W 20010406

AB The invention relates to an oligonucleotide kit as probe for the detection of relevant variations in the DNA methylation of a target group of genes. The invention further relates to the use of the same for detg. the gene variant with regard to DNA methylation, a medical device, using an oligonucleotide kit, a method for detg. the methylation state of an individual and a method for the establishment of a model for establishing the probability of onset of a disease state in an individual. Such diseases may be: undesired pharmaceutical side-effects; cancerous diseases; CNS dysfunctions, injuries or diseases; aggressive symptoms or relational disturbances; clin., psychol. and social consequences of brain injury; psychotic disorders and personality disorders; dementia and/or assocd. syndromes; cardiovascular disease, dysfunction and damage; dysfunction, damage or disease of the gastrointestinal tract; dysfunction, damage or disease of the respiratory system; injury, inflammation, infection, immunity and/or anastasis; dysfunction, damage or disease of the body as an abnormal development process; dysfunction, damage or disease of the skin, muscle, connective tissue or bones; endocrine and metabolic dysfunction, damage or disease; headaches or sexual dysfunction. This abstr. record is one of several records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.

L15 ANSWER 2 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 135:270476 CA
TITLE: Regulation of stearoyl coenzyme A desaturase expression in human retinal pigment epithelial cells by retinoic acid
AUTHOR(S): Samuel, William; Kutty, R. Krishnan; Nagineni, Sahrudaya; Gordon, Joel S.; Prouty, Stephen M.; Chandraratna, Roshantha A. S.; Wiggert, Barbara
CORPORATE SOURCE: Biochemistry Section, Laboratory of Retinal Cell and Molecular Biology, NEI, National Institutes of Health, Bethesda, MD, 20878-2740, USA
SOURCE: J. Biol. Chem. (2001), 276(31), 28744-28750
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Stearoyl-CoA desaturase (SCD) is a regulatory enzyme involved in the synthesis of the monounsatd. fatty acids palmitoleate and oleate. The regulation of SCD is of physiol. importance because the ratio of satd. fatty acids to unsatd. fatty acids is thought to **modulate** membrane fluidity. Differential display anal. of retinal pigment epithelial (ARPE-19) cells identified SCD as a gene regulated by retinoic acid. Two SCD transcripts of 3.9 and 5.2 kilobases in size were found to be expressed in these cells by Northern blot anal. All-trans-retinoic acid (all-trans-RA) increased SCD mRNA expression in a dose- and time-dependent manner, a .apprx.7-fold increase was obsd. with 1 .mu.M all-trans-RA at 48 h. SCD mRNA expression was also increased by 9-cis-retinoic acid (9-cis-RA) as well as 4-(E-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl)benzoic acid (TTNPB), a retinoic acid receptor (RAR)-specific agonist. AGN194301, a **RAR .alpha.**-specific **antagonist**, suppressed the SCD expression induced by all-trans-RA, TTNPB, and 9-cis-RA. These results indicate the involvement of **RAR.alpha.** in the induction of SCD expression by retinoic acid. However, AGN194204, a RXR

(retinoid X receptor) pan agonist, also increased SCD mRNA expression. This increase was not blocked by AGN194301, suggesting that an RAR-independent mechanism may also be involved. Thus, SCD expression in retinal pigment epithelial cells is regulated by retinoic acid, and the regulation appears to be mediated through RAR and RXR.

REFERENCE COUNT: 43

REFERENCE(S):
(1) Bissonnette, R; Mol Cell Biol 1995, V15, P5576 CA
(2) Bok, D; J Cell Sci 1993, V17, P189 CA
(3) Bossie, M; J Bacteriol 1989, V171, P6409 CA
(4) Boylan, J; Mol Cell Biol 1995, V15, P843 CA
(5) Chambon, P; FASEB J 1996, V10, P940 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 21 CA COPYRIGHT 2001 ACS

ACCESSION NUMBER: 134:217982 CA

TITLE: Chromatin-based RAR/RXR heterodimer-regulated transcription system and its use in screening for transcription **modulators**

INVENTOR(S): Chambon, Pierre; Dilworth, F. Jeffrey; Fromental-Ramain, Catherine

PATENT ASSIGNEE(S): Institut National de la Sante et de la Recherche Medicale, Fr.; Centre National de la Recherche Scientifique; Universite Louis Pasteur; Bristol-Myers Squibb Company

SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001016597	A1	20010308	WO 1999-US20018	19990901

W: AU, CA, IL, JP, MX, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

AB The invention relates to methods of identifying agents that interact with retinoic acid receptor (RAR)/retinoid X receptor (RXR) heterodimers. Thus, an in vitro chromatin-based transcription system which enables one to study the mol. events underlying activation of transcription by RXR/RAR heterodimers is demonstrated. The system essentially mimics the in vivo synergistic effect of RAR- and RXR-selective retinoids and the subordination of RXR AF-2 activity to binding of an agonist to RAR.

REFERENCE COUNT: 4

REFERENCE(S):
(1) Evans; US 4981784 A 1991 CA
(2) Evans; US 5906920 A 1999 CA
(3) Mak; US 5714595 A 1998 CA
(4) McKenna; Endocrine Reviews 1999, V20(3), P321 CA

L15 ANSWER 4 OF 21 CA COPYRIGHT 2001 ACS

ACCESSION NUMBER: 134:217577 CA

TITLE: Positive and negative regulation of granulopoiesis by endogenous **RAR.alpha.**

AUTHOR(S): Kastner, Philippe; Lawrence, H. Jeffrey; Waltzinger, Caroline; Ghyselinck, Norbert B.; Chambon, Pierre; Chan, Susan

CORPORATE SOURCE: Institut de Genetique et de Biologie Moleculaire et Cellulaire, Illkirch, 67404, Fr.

SOURCE: Blood (2001), 97(5), 1314-1320

CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acute promyelocytic leukemia (APL) is always assocd. with chromosomal translocations that disrupt the retinoic acid receptor .alpha. (**RAR.alpha.**) gene. Whether these translocations relate to a role for endogenous **RAR.alpha.** in normal granulopoiesis remains uncertain because most studies addressing this question have used non-physiol. overexpression systems. Granulocyte differentiation in cells derived from **RAR.alpha** .-deficient (**RAR.alpha.**-/-) mice was studied and evaluated in the context of agonist-bound and ligand-free **RAR. alpha.**. The authors' results demonstrate that **RAR. alpha.** is dispensable for granulopoiesis, as **RAR. alpha.**-/- mice have a normal granulocyte population despite an impaired ability to respond to retinoids. However, although it is not absolutely required, **RAR.alpha.** can bidirectionally **modulate** granulopoiesis. **RAR.alpha.** stimulates differentiation in response to exogenous retinoic acid. Furthermore, endogenous retinoids control granulopoiesis in vivo, as either vitamin A-deficient mice or animals treated with an RAR **antagonist** accumulate more immature granulocytes in their bone marrow. Conversely, **RAR.alpha.** acts to limit differentiation in the absence of ligand because granulocyte precursors from **RAR.alpha.**-/- mice differentiate earlier in culture. Thus, the block in granulopoiesis exerted by **RAR. alpha.** fusion proteins expressed in APL cells may correspond to an amplification of a normal function of unliganded **RAR. alpha.**.
REFERENCE COUNT: 59
REFERENCE(S): (1) Arnould, C; Hum Mol Genet 1999, V8, P1741 CA
(2) Bauer, A; EMBO J 1998, V17, P4291 CA
(3) Breitman, T; Proc Natl Acad Sci U S A 1980, V77, P2936 CA
(4) Chen, J; Nature 1995, V377, P454 CA
(5) Chen, Z; EMBO J 1993, V12, P1161 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 5 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 132:260009 CA
TITLE: Therapeutic applications for ligands of retinoid receptors
AUTHOR(S): Thacher, Scott M.; Vasudevan, Jayasree; Chandraratna, Roshantha A. S.
CORPORATE SOURCE: Retinoid Research, Department of Biology, Allergan Inc., Irvine, CA, 92623, USA
SOURCE: Curr. Pharm. Des. (2000), 6(1), 25-58
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 216 refs. Synthetic retinoids, ligands for the RAR and RXR members of the steroid/thyroid superfamily of nuclear hormone receptors, are used for the treatment of psoriasis, acne, photoaging and cancer. Retinoid mechanisms of action for these conditions largely involve effects on epithelial differentiation and **modulation** of inflammation with some impact on the immune system. Retinoid medicinal chem. in recent years has identified ligands highly specific for one of the three RAR subtypes (**RAR-.alpha.**) and for the RXR family of

receptors, as well as **antagonists** for the RARs, **RAR**. **alpha**. and the RXRs. Structure-activity relationships among the novel retinoid classes are reviewed along with potential therapeutic activities and side effects. **RAR**-.**alpha**. specific retinoids inhibit cancer cell growth but lack other retinoid toxicities, including skin irritation now ascribed to **RAR**-.**gamma**.. RXR-specific retinoids lower blood glucose in animal models of type 2 diabetes albeit with a potential for mild hypothyroidism. Function-selective retinoids, esp. a class of RAR **antagonists** called inverse agonists, have unexpected gene regulatory activity. Given the diverse properties and tissue distributions of the retinoid receptors, synthesis of addnl. classes of receptor-specific and function-selective ligands has the potential to produce novel therapeutic applications.

L15 ANSWER 6 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 132:232362 CA
TITLE: Follicle-stimulating hormone inhibits all-trans-retinoic acid-induced retinoic acid receptor .alpha. nuclear localization and transcriptional activation in mouse Sertoli cell lines
AUTHOR(S): Braun, Kirt W.; Tribley, Walter A.; Griswold, Michael D.; Kim, Kwan Hee
CORPORATE SOURCE: School of Molecular Biosciences, Center for Reproductive Biology, Washington State University, Pullman, WA, 99164, USA
SOURCE: J. Biol. Chem. (2000), 275(6), 4145-4151
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The regulation of retinoic acid receptor alpha (**RAR**. **alpha**.) signal transduction has not been well characterized. In this study, the authors detd. whether all-trans-retinoic acid (tRA) and FSH **modulate RAR**.**alpha**. receptor subcellular localization, leading to changes in its transcriptional activity and protein expression in mouse Sertoli cell lines. The authors found that tRA induced the nuclear localization of **RAR**.**alpha**. within 30 min and that longer term exposure increased the receptor transcriptional activity and **RAR**.**alpha**. protein expression. Conversely, FSH suppressed the tRA-induced nuclear localization, transcriptional transactivation, and protein expression of **RAR**.**alpha**.. Treatment with two different protein kinase A-selective **antagonists** reversed the inhibitory actions of FSH on tRA-dependent **RAR**.**alpha**. nuclear localization and transcriptional activity. These results are consistent with the involvement of protein kinase A in mediating the inhibitory effects of FSH. For the first time, the authors demonstrate a unique signaling convergence between the **RAR**.**alpha**. and the FSH-mediated signaling pathways, which may have significant implications in the testis because both are crit. regulators of testis physiol.
REFERENCE COUNT: 40
REFERENCE(S): (1) Akmal, K; Biol Reprod 1997, V56, P549 CA
(2) Akmal, K; Endocrinology 1998, V139, P1239 CA
(3) Akner, G; J Steroid Biochem Mol Biol 1995, V52, P1 CA
(4) Chambon, P; FASEB J 1996, V10, P940 CA
(5) Chijiwa, T; J Biol Chem 1990, V265, P5267 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 7 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 131:252998 CA
TITLE: Orphan nuclear hormone receptor RevErb.alpha. **modulates** expression from the promoter of the hydratase-dehydrogenase gene by inhibiting peroxisome proliferator-activated receptor .alpha.-dependent transactivation
AUTHOR(S): Kassam, Altaf; Capone, John P.; Rachubinski, Richard A.
CORPORATE SOURCE: Department of Cell Biology, University of Alberta, Edmonton, AB, T6G 2H7, Can.
SOURCE: J. Biol. Chem. (1999), 274(32), 22895-22900
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peroxisome proliferator-activated receptor .alpha. (PPAR.alpha.) heterodimerizes with the 9-cis-retinoic acid receptor (RXR.alpha.) to bind to peroxisome proliferator-response elements (PPRE) present in the upstream regions of a no. of genes involved in metabolic homeostasis. Among these genes are those encoding fatty acyl-CoA oxidase (AOx) and enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase (HD), the first two enzymes of the peroxisomal .beta.-oxidn. pathway. The orphan nuclear hormone receptor, RevErb.alpha., **modulates** PPAR.alpha./RXR.alpha.-dependent transactivation in a response element-specific manner. In vitro binding anal. showed that RevErb.alpha. bound the HD-PPRE but not the AOx-PPRE. Determinants within the HD-PPRE required for RevErb.alpha. binding were distinct from those required for PPAR.alpha./RXR.alpha. binding. In transient transfections, RevErb.alpha. **antagonized** transactivation by PPAR.alpha./RXR.alpha. from an HD-PPRE luciferase reporter construct, whereas no effects were obsd. with an AOx-PPRE reporter construct. These data identify the HD gene as a target for RevErb.alpha. and illustrate cross-talk between the RevErb.alpha. and PPAR.alpha. signaling pathways on the HD-PPRE. The authors' results suggest a novel role for RevErb.alpha. in regulating peroxisomal .beta.-oxidn.
REFERENCE COUNT: 48
REFERENCE(S): (1) Adelmant, G; Proc Natl Acad Sci 1996, V93, P3553 CA
(2) Besnard, P; FEBS Lett 1993, V327, P219 CA
(3) Bogazzi, F; J Biol Chem 1994, V269, P11683 CA
(4) Castelein, H; J Biol Chem 1994, V269, P26754 CA
(5) Chawla, A; J Biol Chem 1993, V268, P16265 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 8 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 129:326937 CA
TITLE: Method for screening for **modulators** of matrix metalloproteinase gene expression and therapeutic use of **modulators**
INVENTOR(S): Basset, Paul; Anglard, Patrick; Guerin, Eric
PATENT ASSIGNEE(S): Institut National De La Sante Et De La Recherche Medicale, Fr.; Centre National De La Recherche Scientifique; Universite Louis Pasteur; Bristol-Myers Squibb Company
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9848055	A1	19981029	WO 1998-US8346	19980424
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9871603	A1	19981113	AU 1998-71603	19980424
EP 977892	A1	20000209	EP 1998-918732	19980424
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6184256	B1	20010206	US 1998-65904	19980424
PRIORITY APPLN. INFO.:			US 1997-44258 P	19970424
			WO 1998-US8346 W	19980424

AB The present invention relates to methods for identifying and selecting compns. useful in differentially **modulating** the expression of two or more mammalian genes, particularly matrix metalloproteinase (MMP) genes such as those encoding interstitial collagenase (and other genes comprising an AP1-binding site) and stromelysin-3 (and other genes comprising a retinoic acid response element (RARE)). In addn., the invention relates to methods of treating a mammal (such as a human) suffering from or predisposed to a phys. disorder, using pharmaceutical compns. comprising the compns. identified or selected by the above-described methods. The methods of the present invention are useful in treating a variety of phys. disorders in mammals including cancers (particularly carcinomas), inflammatory disorders, fibrotic disorders, ocular disorders and osteoporosis. Thus, studies with natural retinoic acid isomers as well as synthetic retinoids indicated that while the selective activation of either **RAR.alpha**. or **RAR.gamma**. or RXRs substantially repress interstitial collagenase gene expression, the combination of RARs and RXRs is required for optimal stromelysin-3 gene induction and for full repression of interstitial collagenase.

L15 ANSWER 9 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 129:94437 CA
TITLE: Inhibition of activation-induced apoptosis of thymocytes by all-trans- and 9-cis-retinoic acid is mediated via retinoic acid receptor .alpha.
AUTHOR(S): Szondy, Zsuzsa; Reichert, Uwe; Bernardon, Jean-Michel; Michel, Serge; Toth, Reka; Karaszi, Eva; Fesus, Laszlo
CORPORATE SOURCE: Department of Biochemistry, University Medical School of Debrecen, Debrecen, H-4012, Hung.
SOURCE: Biochem. J. (1998), 331(3), 767-774
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thymocytes can be induced to undergo apoptotic cell death by activation through the T-cell receptor (TCR). This process requires macromol. synthesis and has been shown to be inhibited by retinoic acids (RAs). Two groups of nuclear receptors for RAs have been identified: retinoic acid receptors (RARs) and retinoid X receptors (RXRs). All-trans-RA is the high-affinity ligand for RARs, and 9-cis-RA addnl. binds to RXRs with high affinity. Because 9-cis-RA is much more potent in inhibiting TCR-mediated death than all-trans-RA, it was suggested that RXRs participate in the process. In the present study various synthetic retinoid analogs were used to address this question further. The results presented suggest that

the inhibitory effect of RAs on activation-induced death of thymocytes is mediated via **RAR.alpha.**, because (1) it can be reproduced by various **RAR.alpha.** analogs both in vitro and in vivo, (2) the effect of RAs can be inhibited by the addn. of an **RAR.alpha. antagonist**, (3) CD4+ CD8+ thymocytes, which die on TCR stimulation, express **RAR.alpha.**. Stimulation of **RAR.gamma.**, in contrast, enhances the activation-induced death of thymocytes and inhibits its prevention by **RAR.alpha.** stimulation. RXR co-stimulation suspends this inhibitory effect of **RAR.gamma.** and permits the preventive function of **RAR.alpha.** on activation-induced death. The results suggest a complex interaction between the various isoforms of retinoid receptors and demonstrate that low (physiol.) concns. of all-trans-RA do not affect the activation-induced death of thymocytes because the **RAR.alpha.**-mediated inhibitory and the **RAR.gamma.**-mediated enhancing pathways are in balance, whereas if 9-cis-RA is formed, addnl. stimulation of RXRs permits the inhibitory action of **RAR.alpha.**.

L15 ANSWER 10 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 128:149088 CA
TITLE: Acute promyelocytic leukemia: cellular and molecular basis of differentiation and apoptosis
AUTHOR(S): Chen, Zhu; Wang, Zhen-Yi; Chen, Sai-Juan
CORPORATE SOURCE: SHANGHAI INSTITUTE OF HEMATOLOGY AND KEY LABORATORY OF HUMAN GENOME RESEARCH, RUIJIN HOSPITAL, SHANGHAI SECOND MEDICAL UNIVERSITY, SHANGHAI, 200025, Peop. Rep. China
SOURCE: Pharmacol. Ther. (1997), 76(1-3), 141-149
CODEN: PHTHDT; ISSN: 0163-7258
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with many refs. Acute promyelocytic leukemia (APL) accounts for about 10% of all acute myeloid leukemias and is characterized by the chromosomal translocation t(15;17), which fuses the retinoic acid receptor (**RAR**) **.alpha.** gene to the promyelocytic leukemia (PML) gene. The PML-**RAR .alpha.** fusion gene plays an important role in leukemogenesis through **antagonizing** retinoic acid signalling and the regulatory pathways mediated by PML. APL is the first example of a human cancer that can be effectively treated with the differentiation inducer all-trans-retinoic acid (ATRA). The therapeutic effect of ATRA in APL has been assocd. with the direct **modulation** of PML-**RAR .alpha.**, the restoration of the differentiation pathways regulated by wild-type RAR/retinoid X receptor heterodimer and PML. More recently, a second drug, arsenic trioxide (As2O3), has been discovered in China that also has a strong therapeutic effect against APL. As2O3 can induce clin. remission in de novo or relapsed APL patients and has no cross-resistance with ATRA. It has dual effects on APL cells: preferential apoptosis at high concn. (0.5-2 .mu.M) and partial differentiation at low concn. (0.1-0.5 .mu.M). **Modulation** and degrdn. of PML-**RAR .alpha.** proteins can be induced by As2O3 and probably contribute to these two effects. These studies lead to a model in which PML-**RAR .alpha.** could be the target of both ATRA differentiation therapy and As2O3 apoptosis therapy.

L15 ANSWER 11 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 127:355100 CA

TITLE: Retinoid-mediated inhibition of cell growth with stimulation of apoptosis in aggressive B-cell lymphomas
AUTHOR(S): Sundaresan, Alamelu; Claypool, Kent; Mehta, Kapil; Lopez-Berestein, Gabriel; Cabanilias, Fernando; Ford, Richard J., Jr.
CORPORATE SOURCE: Department of Molecular Pathology, University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Cell Growth Differ. (1997), 8(10), 1071-1082
CODEN: CGDIE7; ISSN: 1044-9523
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Retinoids have been shown to **modulate** cell growth and differentiation in a variety of human tumor cell types, but their effects on B-cell non-Hodgkin's lymphomas (NHL-B) have not been explored. In this study, all-trans retinoic acid (ATRA) in the free form and liposome-encapsulated form (L-ATRA) were used to det. effects on fresh NHL-B patient cells as well as cell lines recently established from both HIV-neg. and -pos. NHL-B patient biopsies. Both ATRA and L-ATRA were found to inhibit cell proliferation in NHL-B cells. However, L-ATRA was superior to free ATRA in inhibiting cell proliferation of NHL-B cells and resulted in greater than 90% cell growth inhibition in a dose-dependent manner. In addn., L-ATRA also induced high levels of apoptosis in NHL-B cells in vitro. To delineate the apoptotic pathways involved, the expression of the apoptosis suppressor oncogene bcl-2 was evaluated in different NHL-B cells with and without the t(14;18) chromosomal translocation. After L-ATRA exposure, more than a 50% redn. in the expression of bcl-2 protein was obsd. Bcl-2 message levels were also down-regulated in the L-ATRA-sensitive NHL-B cells. Bax protein levels were analyzed and up-regulated in L-ATRA-sensitive NHL-B cells. Similar results were obsd. in sensitive AIDS/lymphoma cell lines. Expts. using an **RAR-.alpha. antagonist** (RO 41-5253) showed that both the proliferation inhibition and apoptosis induced by L-ATRA could be blocked in NHL-B cells. The findings of the present study indicate that L-ATRA may possess therapeutic potential in blocking cell proliferation, inducing apoptosis, and regulating bcl-2 and bax expression in NHL-B and AIDS/lymphoma cells directly or indirectly.

L15 ANSWER 12 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 127:186127 CA
TITLE: Effects of retinoids on the production of tumor necrosis factor-alpha and nitric oxide by lipopolysaccharide-stimulated rat Kupffer cells in vitro: evidence for participation of retinoid X receptor signalling pathway
AUTHOR(S): Motomura, Kenta; Sakai, Hironori; Isobe, Hidehiko; Nawata, Hajime
CORPORATE SOURCE: Third Department of Internal Medicine, Faculty of Medicine, Kyushu University, Fukuoka, 812-82, Japan
SOURCE: Cell Biochem. Funct. (1997), 15(2), 95-101
CODEN: CBFUDH; ISSN: 0263-6484
PUBLISHER: Wiley
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Kupffer cells play important roles in the development of liver injury by producing cytokines and free radicals. In consequence inhibition of these inflammatory mediators will be one of the targets for treating liver diseases. Retinoids **modulate** a wide variety of functions of monocytes/macrophages. Cellular effects of retinoids are mediated by two

families of nuclear receptors, retinoic acid receptors (RARs) and retinoid X receptors (RXRs). The authors examd. the effects of several kinds of natural and synthetic retinoids on the prodn. of tumor necrosis factor-.alpha. (TNF-.alpha.) and nitric oxide (NO) by LPS-stimulated rat Kupffer cells in vitro. Of the various retinoids tested, 9-cis-retinoic acid (9-cis-RA) and Ro 13-6307, which are agonists of both RARs and RXRs, suppressed the prodn. of TNF-.alpha. and NO in a concn.-dependent fashion, whereas three types of RAR-selective agonists, Ro 13-7410, Ro 40-6055 and Ro 19-0645 did not show any effect. Furthermore, the **RAR**. **alpha**. **antagonist**, Ro 41-5253, did not prevent the effects induced by 9-cis-RA. The results suggest that these effects of 9-cis RA and Ro 13-6307 were induced by the RXRs-dependent signaling pathway.

L15 ANSWER 13 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 125:55070 CA
TITLE: Upregulation of cytokeratins 8 and 18 in human breast cancer T47D cells is retinoid-specific and retinoic acid receptor-dependent
AUTHOR(S): Jing, Yongkui; Zhang, Jie; Waxman, Samuel; Mira-y-Lopez, Rafael
CORPORATE SOURCE: Department Medicine, Mount Sinai School Medicine, New York, NY, 10029, USA
SOURCE: Differentiation (Berlin) (1996), 60(2), 109-117
CODEN: DFFNAW; ISSN: 0301-4681
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mammary gland is chiefly composed of luminal epithelial cells expressing cytokeratins (K) 8, 18 and 19, and basal/myoepithelial cells expressing cytokeratins 5 and 14. Human breast cancer T47D cells have a luminal phenotype and are growth-inhibited by retinoids, a class of compds. known to regulate cytokeratin expression. To further examine retinoid action in breast cancer, the authors have studied the retinoid regulation of cytokeratin expression in the T47D model. Retinoid inhibition of T47D cell growth was accompanied by increases in K8, K18 and K19 mRNA steady-state levels (Northern blot anal.). The effect on K8 was studied in greater detail. This effect was seen with as low as 1 nM all-trans retinoic acid (tRA) and was maximal (up to 7 fold over control) with 1 .mu.M tRA (the highest dose tested). Time-course studies revealed a detectable effect at 1 h and a maximal effect at 8-24 h. Non-retinoidal growth inhibitors (tamoxifen, BrcAMP and genistein) did not **modulate** K8 expression, demonstrating that the effect of tRA was specific. K8 mRNA upregulation was blocked by actinomycin D and cycloheximide, suggesting, in accordance with other studies, that tRA exerted a transcriptional effect that was secondary to de novo protein synthesis. Five retinoids known to activate retinoic acid receptor (RAR) and/or retinoid X receptor (RXR) - tRA; 9-cis-retinoic acid, 9cRA; 13-cis RA, 13cRA; retinyl acetate; and N-(4-hydroxyphenyl) retinamide 4HPR - inhibited T47D cell growth and increased K8 expression, whereas an arotinoid (Ro-40-8757) that is not a RAR activator caused growth inhibition but did not upregulate K8. Activation of **RAR**. **alpha**. contributed to K8 upregulation, since this effect was partially blocked by the **RAR**.**alpha**.-selective **antagonist** Ro-41-5253. Analogous results were obtained throughout when blots were reprobed with K18 cDNA. Western blot and immunocytochem. expts. demonstrated that protein levels of K8 and K18 increased by 2 days of treatment with 1 .mu.M tRA. Thus, retinoids enhance the expression of cognate cytokeratin markers of luminal differentiation in T47D breast cancer cells.

L15 ANSWER 14 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 124:220051 CA
TITLE: Retinoid-induced differentiation of acute promyelocytic leukemia involves PML-**RAR**.**alpha**.-mediated increase of type II transglutaminase
AUTHOR(S): Benedetti, Laura; Grignani, Francesco; Scicchitano, Bianca M.; Jetten, Anton M.; Diverio, Daniela; Lo Coco, Francesco; Avvisati, Giuseppe; Gambacorti-Passerini, Carlo; Adamo, Sergio; et al.
CORPORATE SOURCE: Inst. Histology General Embryology, University Rome "La Sapienza", Rome, 00161, Italy
SOURCE: Blood (1996), 87(5), 1939-50
CODEN: BLOOAW; ISSN: 0006-4971
DOCUMENT TYPE: Journal
LANGUAGE: English
AB All-trans retinoic acid (t-RA) administration leads to complete remission in acute promyelocytic leukemia (APL) patients by inducing growth arrest and differentiation of the leukemic clone. In the present study, we show that t-RA treatment dramatically induced type II transglutaminase (type II TGase) expression in cells carrying the t(15;17) translocation and expressing the PML-**RAR**.**alpha**. product such as the APL-derived NB4 cell line and fresh leukemic cells from APL patients. This induction correlated with the t-RA-induced growth arrest, granulocytic differentiation, and upregulation of the leukocyte adherence receptor .beta. subunit (CD18) gene expression. The increase in type II TGase was not abolished by cycloheximide treatment, suggesting that synthesis of a protein intermediate was not required for the induction. T-RA did not significantly alter the rate of growth arrest and did not stimulate differentiation and type II TGase activity in NB4.306 cells, a t-RA-resistant subclone of the NB4 cell line, or in leukemic cells derived from two patients morphol. defined as APL but lacking the t(15; 17). However, in NB4.306 cells, t-RA treatment was able to increase CD18 mRNA expression in a manner similar to NB4 cells. The mol. mechanisms involved in the induction of these genes were investigated. NB4 cells, using novel receptor-selective ligands such as 9-cis-RA, TTNPB, AM580, and SR11217, we found that RAR- and **RAR**.**alpha**.-selective retinoids were able to induce growth arrest, granulocytic differentiation, and type II TGase, whereas the RXR-selective retinoid SR11217 was inactive. Moreover, an **RAR**.**alpha**.-**antagonist** completely inhibited the expression of type II TGase and CD18 induced by these selective retinoids in NB4 cells. In NB4.306 cells, an **RAR**.**alpha**.-dependent signaling pathway was found involved in the **modulation** of CD18 expression. In addn., expression of the PML-**RAR**.**alpha**. gene in myeloid U937 precursor cells resulted in the ability of these cells to induce type II TGase in response to t-RA. On the basis of these results we hypothesize a specific involvement of a signaling pathway involving PML-**RAR**.**alpha**. for the induction of growth arrest, granulocytic differentiation, and type II TGase by retinoids in APL cells.

L15 ANSWER 15 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 124:137529 CA
TITLE: Functional **antagonism** between the retinoic acid receptor and the viral transactivator BZLF1 is mediated by protein-protein interactions
AUTHOR(S): Pfitzner, Edith; Becker, Peter; Rolke, Andreas; Schuele, Roland
CORPORATE SOURCE: Inst. Experimentelle Krebsforschung, Univ. Freiburg, Freiburg, 79106, Germany

SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1995), 92(26), 12265-9
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Epstein-Barr virus-encoded protein BZLF1 is a member of the basic leucine zipper (bZip) family of transcription factors. Like several other members of the bZip family, transcriptional activity of BZLF1 is **modulated** by retinoic acid receptors (RARs). We present evidence that the **RAR.alpha.** and BZLF1 can reciprocally repress each other's transcriptional activation by a newly discovered mechanism. Anal. of **RAR.alpha.** mutants in transfection studies reveals that the DNA binding domain is sufficient for inhibition of BZLF1 activity. Anal. of BZLF1 mutants indicates that both the coiled-coil dimerization domain and a region contg. the transcriptional activation domain of BZLF1 are required for transrepression. Coimmunopptn. expts. demonstrate phys. interactions between **RAR.alpha.** and BZLF1 in vivo. Furthermore, glutathione S-transferase-pulldown assays reveal that these protein-protein interactions are mediated by the coiled-coil dimerization domain of BZLF12 and the DNA binding domain of **RAR.alpha.**. While **RAR.alpha.** is unable to recognize BZLF1 binding sites, the **RAR.alpha** . can be tethered to the DNA by forming a heteromeric complex with BZLF1 bound to DNA. Tethering RARs via protein-protein interactions onto promoter DNA suggest a mechanism through which RARs might gain addnl. levels of transcriptional regulation.

L15 ANSWER 16 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 123:219221 CA
TITLE: Coordinated up-regulation of choline acetyltransferase and vesicular acetylcholine transporter gene expression by the retinoic acid receptor .alpha., cAMP, and leukemia inhibitory factor/ciliary neurotrophic factor signaling pathways in a murine septal cell line
AUTHOR(S): Berse, Brygida; Blusztajn, Krzysztof
CORPORATE SOURCE: Dep. Pathol. Psychiatry, Boston Univ. Sch. Med., Boston, MA, 02118, USA
SOURCE: J. Biol. Chem. (1995), 270(38), 22101-4
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The proteins responsible for acetylcholine (ACh) synthesis (choline acetyltransferase, ChAT) and storage (vesicular ACh transporter, VAChT) are encoded by two closely linked genes in vertebrates, with the VAChT coding sequence contained within the first intron of the ChAT gene. This unusual genomic organization suggests that the transcription of these two genes is coordinately regulated. Using Northern anal. the authors studied the **modulation** of ChAT and VAChT expression in a murine septal cell line (SN56) by three groups of agents: retinoids, trophic factors belonging to the leukemia inhibitory factor/ciliary neurotrophic factor (LIF/CNTF) family, and cAMP. All-trans-retinoic acid increased both ChAT and VAChT mRNA levels in SN56 cells up to 3.5-fold, and elevated intracellular ACh levels by 2.5-fold. This effect was mimicked by a retinoic acid receptor .alpha. (**RAR.alpha.**) agonist (Ro 40-6055) and prevented by a specific **antagonist** (Ro 41-5253), indicating that it was mediated by **RAR.alpha** .. ChAT- and VAChT-specific transcripts were also induced (up to 3-fold) by treatment with CNTF or LIF (20 ng/mL, 48 h), as well as by dibutyryl cAMP (1 mM). All these agents increased the ACh level in the cells (up to

2.5-fold). Dibutyryl cAMP had a greater effect on the level of VAChT mRNA (4-fold induction) than on the level of ChAT mRNA (2-fold induction), suggesting a quant. differential transcriptional regulation of the two genes by the cAMP pathway. The effects of the three groups of agents studied on ChAT and VAChT mRNA levels were additive, pointing to several independent mechanisms by which the cholinergic properties of septal neurons can be **modulated**.

L15 ANSWER 17 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 123:48425 CA
TITLE: All-trans- and 9-cis-retinoic acid enhance the cholinergic properties of a murine septal cell line: evidence that the effects are mediated by activation of retinoic acid receptor-.alpha.
AUTHOR(S): Pedersen, Ward A.; Berse, Brygida; Schueler, Ulrike; Wainer, Bruce H.; Blusztajn, Jan Krzysztof
CORPORATE SOURCE: Departments of Pathology and Psychiatry, Boston University School of Medicine, Boston, MA, USA
SOURCE: J. Neurochem. (1995), 65(1), 50-8
CODEN: JONRA9; ISSN: 0022-3042
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors investigated the effects of retinoids on the cholinergic properties of a murine septal cell line, SN56. Treatment of the cells with all-trans-retinol (vitamin A), all-trans-retinal, all-trans-retinoic acid (t-RA), 9-cis-retinoic acid (9c-RA), or 13-cis-retinoic acid caused time- and concn.-dependent increases in choline acetyl-transferase activity (up to 3.4-fold) and in intracellular acetylcholine levels (up to 2.5-fold, with resp. EC50 values of 68, 50, 18, 15, and 56 nM). Furthermore, treatment with either t-RA or 9c-RA at 1 .mu.M for 48 h resulted in an increase in the expression of choline acetyltransferase mRNA by threefold that of controls. These data and the presence of putative retinoic acid response elements in the 5' region of the murine choline acetyltransferase gene indicate that retinoids stimulate choline acetyltransferase transcription in murine cholinergic neurons. No additivity or synergism was obsd. between the effects of t-RA and 9c-RA on any of these cholinergic properties of SN56 cells, suggesting a common mechanism of action of the two retinoids. However, a combined treatment with t-RA and forskolin, which activates adenylate cyclase, resulted in an additive increase in acetylcholine content. Using an **antagonist** selective for the retinoic acid receptor-.alpha. subtype, Ro 41-5253, the authors found that the effects of t-RA and 9c-RA on the acetylcholine levels were abolished. An agonist selective for retinoic acid receptor-.alpha., Ro 40-6055, increased acetylcholine levels to a similar extent as t-RA and 9c-RA, and this effect was blocked by the **antagonist**. The results suggest that retinoids **modulate** the cholinergic phenotype of septal neurons by activation of retinoic acid receptor-.alpha..

L15 ANSWER 18 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 123:47169 CA
TITLE: Retinoic acid and acute promyelocytic leukemia: A model of targetting treatment for human cancer
AUTHOR(S): Chen, Zhu; Chen, Sai-Juan; Wang, Zhen-Yi
CORPORATE SOURCE: Rui Jin Hospital, Shanghai Second Medical University, Shanghai, 200025, Peop. Rep. China
SOURCE: C. R. Acad. Sci., Ser. III (1994), 317(12), 1135-41
CODEN: CRASEV; ISSN: 0764-4469
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 68 refs. Acute promyelocytic leukemia (APL) is the first example among the human malignancies that responds to differentiation therapy, in that complete remission (CR) can be achieved in up to 90 % of patients by using a differentiation inducer, all-trans retinoic acid (ATRA). The specific chromosomal translocation t(15;17) in APL has been shown to fuse the gene for the retinoic acid receptor .alpha. (**RAR .alpha.**) with a chromosome 15q locus, PML. Alterations to the **RAR.alpha.** and the PML gene structures in the t(15;17) have been characterized and used as specific mol. marker for diagnosis of the disease. PML/**RAR.alpha.** **antagonizes** wild-type PML and RXR and could block the differentiation pathways mediated by these two regulators. A variant translocation t(11;17) has also been discovered in a subset of APL which fuses **RAR. alpha.** to a new gene, PLZF on chromosome 11q23. Both PML/ **RAR.alpha.** and PLZF/**RAR.alpha.** display the "dominant neg." effect on the wild-type RAR/RXR. However, t(11;17) APL patients differ from t(15;17) APL in that they respond poorly to ATRA. Morphol. defined APL cases which however do not have PML/ **RAR.alpha.** generally show no response to ATRA. Recently it has been shown that PML/**RAR.alpha.** can be **modulated** directly by ATRA. All these data support the idea that PML/**RAR.alpha.** is a specific target of ATRA which can overcome the differentiation block imposed by PML/**RAR. alpha.**. The ATRA treatment of APL thus further reinforces the concept of differentiation therapy.

L15 ANSWER 19 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 121:132152 CA
TITLE: **Modulation** of fibronectin and thymic stromal cell-dependent thymocyte maturation by retinoic acid
AUTHOR(S): Meco, Daniela; Scarpa, Susanna; Napolitano, Maddalena; Maroder, Marella; Bellavia, Diana; De Maria, Ruggero; Ragano-Caracciolo, Maria; Frati, Luigi; Modesti, Andrea; et al.
CORPORATE SOURCE: Dep. Experimental Med., Univ. La Sapienza, Rome, Italy
SOURCE: J. Immunol. (1994), 153(1), 73-83
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Retinoic acid (RA) controls the differentiation of a variety of cell types, although its role in influencing T cell development and the mechanisms potentially involved have not been thoroughly investigated. To study the ability of RA to **modulate** T cell development, the authors established a thymic cell line (TC-1S) that supports the phenotypic maturation of CD4-8- double neg. (DN) or CD3-4-8- triple neg. (TN) thymocyte precursors. Cocultures of either DN or TN thymocytes on a monolayer of TC-1S cells resulted in the appearance of thymocytes with a more mature phenotype (CD4+8+ double pos., CD4+ or CD8+ single pos., and CD3low cells). Double neg. T cell contact with TC-1S cells also increased the prodn. of fibronectin (FN) by the thymic stroma and the expression of the VLA-4 FN receptor on the DN cells. Ab-mediated inhibition of the interaction between FN and its receptors significantly reduced the level of induced T cell maturation. Addn. of RA either to TC-1S cells alone or to the coculture with DN cells decreased stromal cell FN expression, **antagonized** DN cell-induced increase in stromal cell FN prodn. and significantly inhibited in vitro thymocyte maturation. The effects RA were likely mediated by RA acid receptors .alpha. and .gamma. expressed both in DN thymocytes and TC-1S cells. Together these data suggest that FN/VLA-4 interaction may be an important component of stromal cell-dependent thymocyte phenotypic differentiation and that this

interaction can be one of the targets for the influence of RA in T cell development.

L15 ANSWER 20 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 120:125937 CA
TITLE: A protein kinase C-dependent activity **modulates** retinoic acid-induced transcription
AUTHOR(S): Tahayato, Ali; Lefebvre, Philippe; Formstecher, Pierre; Dautrevaux, Michel
CORPORATE SOURCE: Fac. Med. Lille, Lille, 59045, Fr.
SOURCE: Mol. Endocrinol. (1993), 7(12), 1642-53
CODEN: MOENEN; ISSN: 0888-8809
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The retinoic acid receptors (RARs) and retinoid X receptors, which are members of the nuclear receptor family, mediate the effects of vitamin A derivs. on cellular growth and differentiation. The protein kinase C isoenzyme family also controls these processes in response to extracellular stimuli. The authors have investigated the relation between these two signal transducing pathways using gene transfer techniques. The authors show that selective inhibition. of protein kinase C (PKC) and its depletion by prolonged treatment with 12-O-tetradecanoylphorbol-13-acetate lead to the loss of ligand-dependent transcription of an RA-inducible promoter. The effect of the depletion in cellular PKC could be counteracted by overexpression of PKC.alpha. and is directly correlated to the loss of the DNA-binding activity of complexes contg. the human **RAR.alpha**. (hRAR.alpha.). Indirect immunofluorescence studies demonstrated an altered subcellular localization of hRAR.alpha.. However, direct in vitro phosphorylation of hRAR.alpha. by PKC diminished its ability to form heterodimeric or homodimeric complexes on a retinoic acid response element, suggesting that the DNA-binding capacity of hRAR.alpha. in intact cells is directly controlled by a PKC-dependent mechanism. Thus the authors' observations establish a functional link between the PKC and retinoid pathways, which are generally considered to have **antagonistic** activities on differentiation processes.

L15 ANSWER 21 OF 21 CA COPYRIGHT 2001 ACS
ACCESSION NUMBER: 117:144230 CA
TITLE: Retinoid **antagonism** of estrogen-responsive transforming growth factor .alpha. and pS2 gene expression in breast carcinoma cells
AUTHOR(S): Fontana, Joseph A.; Nervi, Clara; Shao, Zhi Ming; Jetten, Anton M.
CORPORATE SOURCE: Cancer Cent., Univ. Maryland, Baltimore, MD, 21218, USA
SOURCE: Cancer Res. (1992), 52(14), 3938-45
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Exposure of MCF-7 breast carcinoma cells to estradiol results in an increase in transforming growth factor a (TGF-.alpha.) synthesis and secretion. Since TGF-.alpha. is a potent inducer of proliferation in MCF-7 cells, the increase in TGF-.alpha. prodn. by estradiol is thought to play an important role in the estrogen stimulation of growth of these cells. Retinoic acid inhibits the proliferation of MCF-7 cells and **antagonizes** the estrogen stimulation of growth. Addn. of retinoic acid resulted in a > 70% inhibition of estradiol-induced TGF-.alpha. synthesis and secretion in MCF-7 cells. The increase in TGF-.alpha. mRNA expression by estradiol was also inhibited by exposure of the cells to retinoic acid. Pretreatment of the cells with retinoic acid for 24 or 72

h caused > 50 and 90% inhibition, resp., of the estradiol-enhanced expression of TGF-.alpha. mRNA. Expression of pS2 mRNA in MCF-7 cells was stimulated approx. 8-fold by estradiol. Retinoic acid treatment suppressed by > 80% both the basal and estradiol-induced pS2 mRNA expression. Retinoic acid **modulation** of the estrogen receptor gene mRNA was not responsible for the retinoic acid inhibition of the stimulation of pS2 and TGF-.alpha. gene expression by estradiol, since estrogen receptor gene expression was increased rather than decreased in the presence of retinoic acid. The nuclear retinoic acid receptors .alpha. and .gamma. mRNA were expressed in MCF-7 cells and its retinoic acid-resistant deriv. RROI. Addn. of estradiol to MCF-7 cells resulted in a decreased expression of retinoic acid receptor .gamma. mRNA; this redn. is prevented by the presence of retinoic acid. These results indicate that retinoic acid can inhibit estradiol-induced TGF-.alpha. and pS2 mRNA expression in MCF-7 cells. The suppression of TGF-.alpha. expression may represent one possible mechanism by which retinoic acid **antagonizes** the stimulation of MCF-7 proliferation by estradiol.

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(FILE 'HOME' ENTERED AT 14:51:20 ON 20 NOV 2001)

FILE 'CA' ENTERED AT 14:57:10 ON 20 NOV 2001

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L1          362 S RAR AND MODULAT?
L2      1995134 S B OR BETA
L3         1365 S L2 AND RAR
L4         1009 S RAR (2A) L2
L5          149 S L1 AND L4
L6           16 S L5 AND ANTAGON?
L7         1971 S RAR.ALPHA. OR RAR.GAMMA. OR RAR.BETA.
L8         1503 S RAR.ALPHA.
L9         1971 S RAR.ALPHA. OR RAR.GAMMA. OR RAR.BETA.
L10         625 S RAR.GAMMA.
L11         918 S RAR.BETA.
L12        1971 S L8 OR L10 OR L11
L13         213 S L12 AND ANTAGON?
L14         198 S L13 NOT L6
L15          21 S L14 AND MODULAT?
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Executing the logoff script...

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STN INTERNATIONAL LOGOFF AT 15:06:57 ON 20 NOV 2001